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Differential Time Course of Microstructural White Matter in Patients With Psychotic Disorder and Individuals at Risk: A 3-Year Follow-up Study

Patrick Domen^{*1}, Sanne Peeters^{1,2}, Stijn Michielse¹, Ed Gronenschild¹, Wolfgang Viechtbauer¹, Alard Roebroeck³, Jim van Os^{1,4}, Machteld Marcelis^{1,5}, for Genetic Risk and Outcome of Psychosis (G.R.O.U.P.)

¹Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands; ²Faculty of Psychology and Educational Sciences, Open University of the Netherlands, Heerlen, The Netherlands; ³Department of Cognitive Neuroscience, Maastricht University, Maastricht, The Netherlands; ⁴King's College London, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, London, UK; ⁵Institute for Mental Health Care Eindhoven (GGzE), Eindhoven, The Netherlands

*To whom correspondence should be addressed; Department of Psychiatry and Neuropsychology, Maastricht University Medical Centre, PO Box 616 (location Vijverdal), 6200 MD Maastricht, The Netherlands; tel: +31-43-388-3968, fax: +31-43-388-4122, e-mail: p.domen@maastrichtuniversity.nl

Background: Although widespread reduced white matter (WM) integrity is a consistent finding in cross-sectional diffusion tensor imaging (DTI) studies of schizophrenia, little is known about the course of these alterations. This study examined to what degree microstructural WM alterations display differential trajectories over time as a function of level of psychosis liability. **Methods:** Two DTI scans with a 3-year time interval were acquired from 159 participants (55 patients with a psychotic disorder, 55 nonpsychotic siblings and 49 healthy controls) and processed with tract-based spatial statistics. The mean fractional anisotropy (FA) change over time was calculated. Main effects of group, as well as group \times region interactions in the model of FA change were examined with multilevel (mixed-effects) models. **Results:** Siblings revealed a significant mean FA decrease over time compared to controls ($B = -0.004$, $P = .04$), resulting in a significant sibling-control difference at follow-up ($B = -0.007$, $P = .03$). Patients did not show a significant change over time, but their mean FA was lower than controls both at baseline and at follow-up. A significant group \times region interaction ($\chi^2 = 105.4$, $P = .01$) revealed group differences in FA change in the right cingulum, left posterior thalamic radiation, right retrolenticular part of the internal capsule, and the right posterior corona radiata. **Conclusion:** Whole brain mean FA remained stable over a 3-year period in patients with psychotic disorder and declined over time in nonaffected siblings, so that at follow-up both groups had lower FA with respect to controls. The results suggest that liability for psychosis may involve a process of WM alterations.

Key words: psychotic disorder/diffusion tensor imaging/disease progression/siblings

Introduction

The functional dysconnectivity hypothesis of schizophrenia suggests that symptoms originate as a result of miscommunication between different brain areas,^{1,2} associated with microstructural white matter (WM) alterations. Diffusion tensor imaging (DTI) is used to identify potential WM microstructural correlates. Fractional anisotropy (FA) combines information on myelination, fiber density, and number of axons in 1 measure, whereas additional diffusion parameters (axial-, radial-, and mean diffusivity) may provide more specific information on WM integrity.³ A large number of cross-sectional DTI studies of patients in early and later stages of schizophrenia have shown decreased FA with respect to controls in several WM tracts throughout the brain.^{4,5} However, it is not clear when these WM alterations occur and how they develop over time.⁶ Both a neurodevelopmental model,^{7,8} implying that WM alterations are present before disease onset and a postonset progression model, indicating that structural brain abnormalities progress over time after disease onset, have been proposed.^{9,10} In support of the neurodevelopmental model, several cross-sectional DTI studies have revealed microstructural WM alterations in frontotemporal and -parietal connections in first-degree relatives without symptoms,^{11,12} in clinical high-risk populations before onset,^{13,14} and in patients with early onset psychosis.¹⁵ Indeed, the lifetime trajectory of WM alterations in schizophrenia suggests higher percentages of WM loss in the first years of

the illness, implicating altered neurodevelopment.^{6,16} The literature on longitudinal WM changes, however, is too limited to draw firm conclusions on neurodevelopmental or progressive changes, as well as the role of medication.¹⁶ A study by Carletti and colleagues (2012) showed a significant progressive reduction in FA in the left frontal WM in individuals at “Ultra-High Risk” (UHR) who developed psychosis compared to UHR subjects who did not make a “transition”.¹⁷ Reis Marques and colleagues (2014) found an increase in FA in first episode patients (both responders and nonresponders to antipsychotic [AP] medication) over a 12-week period,¹⁸ and Garver and colleagues (2008) reported reduced mean diffusivity after 28 days of treatment in drug-responding patients with schizophrenia, which was not found in nonresponders.¹⁹ A fourth study compared WM FA changes between individuals during a more chronic course of schizophrenia ($n = 49$) and healthy controls ($n = 16$), reporting a stronger FA decline over 4 years in frontal, temporal, and parietal WM in the controls. A subgroup of patients with poor outcome could be differentiated from a group with good outcome by regional progression of WM alterations in an adjacent precentral/postcentral area.²⁰

Not only DTI, but also longitudinal volumetric studies are scarce. Decreases over time have been described in recent onset and first-episode patients in frontal lobe WM volume²¹ and temporal lobe WM volume, respectively.²² However, in patients aged up to 51 years, van Haren and colleagues (2008) described an abnormal curved trajectory of volume change, with normalization of age-related volume change later in life.²³

In our recent cross-sectional diffusion analyses of patients with a psychotic disorder, siblings and controls ($n = 258$), patient-specific microstructural WM alterations were found in the corpus callosum and other WM tracts.²⁴ This sample was re-scanned approximately 3 years later to examine whether the evolution of FA over time varies as a function of familial risk for psychotic disorder.

Methods

Participants

Participants were recruited in the context of a multicenter longitudinal study (Genetic Risk and Outcome of Psychosis, G.R.O.U.P.) in the Netherlands.²⁵ The magnetic resonance imaging (MRI) add-on study was conducted in Maastricht, the Netherlands (see Domen and colleagues²⁴ or the Supplemental Method section for full information on in- and exclusion criteria of the participants and diagnostic assessments). For the baseline MRI study, 300 participants were included of which 258 provided a valid DTI scan: 85 patients with a psychotic disorder, 93 siblings without a psychotic disorder, and 80 healthy controls. At follow-up, approximately 3 years later (mean: 3.3 year), a second DTI scan was acquired from 180 participants (loss to follow-up of 40%). The

final sample comprised 159 participants (55 patients with a psychotic disorder, 55 siblings without a psychotic disorder, and 49 healthy controls), for which a pair of DTI scans was available for longitudinal analysis (table 1).

The sample included 129 families of which 16 families contributed 1 patient and 1 healthy sibling and 1 family contributed 1 patient and 2 healthy siblings. Six families contributed 2 healthy siblings, 1 family contributed 3 healthy siblings, and 4 families contributed 2 healthy controls. In addition, 38 families contributed 1 patient, 22 families contributed 1 sibling, and 41 families contributed 1 control.

The standing ethics committee approved the study protocol, and all participants gave written informed consent in accordance with the committee's guidelines.

Measures

Symptoms. At both time points, symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS).²⁶ The 5-factor model by van der Gaag and colleagues (2006) was used, dividing the PANSS in positive symptoms, negative symptoms, disorganization symptoms, excitement, and emotional distress.²⁷ The scores of the individual items of the 5 symptom dimensions were summed. To assess clinical remission, the operationalized criteria described by Andreasen and colleagues (2005)²⁸ were applied.

Educational level (at baseline) was defined as the highest accomplished level of education. Handedness was assessed using the Annett Handedness Scale.²⁹

Medication. In the patient group, AP medication use was determined by patient report and verified with the treating consultant psychiatrist. Best estimate lifetime (cumulative) AP use at baseline was determined by multiplying the number of days of AP use with the corresponding haloperidol equivalents and summing these scores for all periods of AP use (including the exposure period between baseline assessment for the G.R.O.U.P. study and the moment of baseline MRI scanning), using the published converting formulas for AP dose equivalents described by Andreasen and colleagues.³⁰ The same procedure was used for calculating cumulative AP exposure during the 3-year follow-up period.

Substance Use. Substance use was measured at both time points with the Composite International Diagnostic Interview (CIDI) sections B-J-L.³¹ Alcohol use was defined as the reported number of weekly consumptions during the last 12 months. As data on drug use of the last 3 years were not available, cannabis and other drugs were assessed as reported frequency of use during the last 12 months, as well as lifetime use. CIDI frequency data on alcohol, lifetime cannabis, and other drug use were available at baseline for respectively 158 participants (1% missing data), 155 participants (3% missing data), and 157 participants (1% missing data).

Table 1. Demographic Characteristics of the Participants ($n = 159$)

Time Point	Controls ($n = 49$)		Siblings ($n = 55$)		Patients ($n = 55$)	
	0	1	0	1	0	1
Scan interval (d)	1222 ± 198		1177 ± 101		1196 ± 121	
Age at scan (y)	31.0 ± 11.0	34.4 ± 10.9	30.9 ± 8.5	34.1 ± 8.5	28.7 ± 6.3	32.0 ± 6.2
Sex, male (%)	19 (39%)		29 (53%)		40 (73%)	
Handedness	83.2		78.0		72.2	
Level of education	5.4 ± 2.0		5.4 ± 2.1		4.5 ± 1.9	
Age of onset (y)	—		—		21.8 ± 6.3	
Illness duration (y)	—		—		5.7 ± 3.5	10.3 ± 4.0
AP medication	—		—		6693 ± 6254 ^a	5335 ± 5715 ^b
Diagnosis						
Schizophrenia	—		—		33	
Schizoaffective disorder	—		—		16	
Psychotic disorder NOS	—		—		6	
Major depressive disorder ^c	11		15		—	
Substance use						
Cannabis		4.8 ± 32.0 ^d		7.1 ± 49.1 ^d		36.5 ± 105.2 ^d
Other drugs		0.0		0.0		15.2 ± 57.0 ^d
Alcohol		6.3 ± 10.8 ^e		6.0 ± 5.4 ^e		4.9 ± 7.6 ^e
PANSS scores						
Positive symptoms	7.3 ± 1.2	7.4 ± 0.8	7.4 ± 0.9	7.4 ± 0.7	9.6 ± 3.7	11.6 ± 5.7
Negative symptoms	8.2 ± 1.2	8.0 ± 0.2	8.2 ± 1.3	8.0 ± 0.3	11.4 ± 5.2	11.1 ± 4.2
Disorganization	10.3 ± 1.5	10.1 ± 0.3	10.3 ± 0.6	10.1 ± 0.4	11.7 ± 2.6	11.8 ± 2.5
Excitement	8.4 ± 1.3	8.3 ± 0.5	8.5 ± 1.2	8.3 ± 0.6	9.4 ± 1.9	9.7 ± 2.5
Emotional distress	9.3 ± 2.1	9.4 ± 1.7	9.7 ± 2.2	9.7 ± 2.2	12.9 ± 5.2	14.1 ± 5.0
Remission (percentage)	—	—	—	—	61%	62%

Note: Means ± SDs are reported. AP, antipsychotic; NOS, not otherwise specified; PANSS, Positive and Negative Syndrome Scale.

^aCumulative exposure (in haloperidol equivalents), lifetime until baseline assessment.

^bExposure (in haloperidol equivalents) over last 3 y.

^cHistory of major depressive disorder, no current episodes at baseline or in last 3 y.

^dMean number of times; last 12 mo.

^eWeekly consumptions last 12 mo.

Image Acquisition

MRI scans were obtained at Maastricht University, the Netherlands, using an Allegra Magnetom MR (Siemens) operating at 3.0 Tesla. At both measurement points, microstructural anatomy was examined using DTI with an echo-planar-imaging sequence (field of view 230 × 230 mm², TR 10800 ms, TE 84 ms, voxel size 1.8 × 1.8 × 1.8 mm³, *b*-value 1000 s/mm², 85 slices, no overlap). As a result of a scanner update at the baseline measurement, 2 DTI sequences were used: one with 76 directions (of which 4 diffusion-unweighted [B0] and 72 diffusion-weighted [B1000]) and one with 81 directions (8xB0 and 73xB1000). A potential association between the proportion of baseline scans and group was investigated using a *Pearson chi-square* test. At follow-up, the DTI sequence comprised 81 directions (8xB0 and 73xB1000). Total acquisition time of the DTI sequence was 15 minutes.

DTI Analysis

DTI data were processed using tract-based spatial statistics (TBSS) v1.2 in FSL 4.1.6 (FMRIB Analysis Group, <http://www.fmrib.ox.ac.uk/analysis/research/tbss>). First,

standard Siemens DICOM files were transformed into compressed NIFTI format using a custom built in-house software named GIANT (General Image ANALysis Tools developed by E.G.). Raw data were corrected for head movement and eddy currents invoked during scanning. The B0 volume was skull-stripped using FSL's Brain Extraction Tool³² and this served as a brain mask for all B volumes.

The next step was fitting a diffusion tensor model at each voxel using data output from the brain extraction, diffusion weighted data, and gradient directions following a general linear model (FreeSurfer v4.5.0, <http://www.freesurfer.net>). After tensor fitting (using the DT-Recon script) the process continued working on FA volumes, eroding them slightly. Nonlinear registration aligned each FA volume to 1 × 1 × 1 mm standard FMRIB58_FA space. The standard FMRIB58_FA contains a template derived from high-resolution images of 58 participants in a well-aligned population (both males and females ranging between 20 and 50 years of age).³³

After nonlinear transformation of the FA volumes into standard space, 2 mean FA skeletons were created; (1) one based on 3 groups ($n = 159$: controls, siblings,

patients) for the cross-sectional analysis at follow-up and (2) one based on 6 groups (3 groups \times 2 time-points) for the longitudinal analysis. The mean FA skeleton follows the major WM tracts in each individual participant (normalized in MNI152 space) and provides a way to compare between (groups of) participants. The FA threshold was set, using visual inspection of the FA skeleton, at a level of 0.25, to include major WM tracts whilst removing small peripheral tracts that would cause excess inter-participant variability. In addition, this threshold setting avoided inclusion of regions that are likely to be composed of multiple tissue types or fiber orientations. In the final step, a binary skeleton mask was created and used to extract FA values of the individual participants. The Johns Hopkins University International Consortium for Brain Mapping (JHU ICBM)-DTI-81 WM atlas labels³⁴ were used to label all voxels and assign a specific tract name. If the voxels did not match with the JHU ICBM labels, they were identified using the JHU WM tractography atlas.³⁵

Statistical Analyses

From the 38 JHU labeled WM tracts, skeleton mean FA values per participant per time point were extracted and exported to R (version 3.2.0), a free software environment for statistical computing and graphics.³⁶

Longitudinal Analyses. Within-group paired *t*-tests were done to examine the difference in regional mean FA between baseline and follow-up. Subsequently, a mean FA “change” (delta, Δ per participant per region) was calculated by subtracting mean FA (baseline) from mean FA (follow-up). The data set was transformed from a wide to a hierarchically structured data set, with 38 regional Δ FA measures (Level 1) nested in subjects (Level 2) who were part of the same families (Level 3). A mixed-effects model was used to examine the model with Δ FA measures as the dependent variable and scan-interval as additional covariate. In addition, since the outcome represents means based on varying number of voxels (depending on the region), we used a model in which the error variance for a particular observation was inversely weighted by the number of voxels within the corresponding region (ie, since the variance of a mean is equal to the variance of a single observation—in this case voxel—divided by the number of values used for the averaging). Main effects of group, corrected for age, sex, handedness, level of education and scan-interval, as well as group \times sex and group \times region interactions in the model of Δ FA were examined. In each of the 38 regions, between-group factor significance was tested. Regions with a significant group effect were examined with pairwise comparisons (ie, it was tested whether Δ FA differed between patients and controls, between siblings and controls, and between patients and siblings).

Due to the large number of regions (and hence tests), Simes’ procedure^{37,38} was used to control the false discovery rate when testing the regional within-group mean FA differences between baseline and follow-up, the between-group effects within the 38 regions, and the pairwise comparisons.

Sensitivity analyses were performed with last year cannabis use, lifetime cannabis use, and scan type (76 or 81 directions) as additional covariates in 3 separate models. Since a subgroup of participants in the control ($n = 11$) and sibling group ($n = 15$) had a history of a depressive disorder (and a number of DTI studies with patients with a major depressive disorder have shown decreased FA in several cortical and subcortical WM tracts³⁹), additional sensitivity analyses were conducted controlling for history of depression.

AP Medication. In patients only, the association between Δ FA and respectively last 3-year and lifetime AP use was examined. These variables were entered both as linear and as factored variables (ie, representing the distribution of scores divided by its tertiles: low, moderate, or high AP exposure), allowing visualization of dose-response. Sensitivity analyses were done using patient subgroups (with low, moderate, and high AP exposure), ie, the association between group and Δ FA was examined per AP subgroup to examine whether patients with differential AP exposure would have differential FA change over time in comparison to controls and siblings.

Cross-sectional Analyses at Follow-up. To examine group differences at follow-up ($n = 159$), a whole-brain mean FA was computed with the 38 WM regions conform the above-described procedure. Whole-brain FA was the dependent variable and random effects (intercepts) were added for each subject and family, including a priori hypothesized confounding variables age, sex, handedness, and level of education as fixed effects.

Results

Participant Characteristics

The characteristics of the 159 individuals with a baseline and follow-up scan are displayed in [table 1](#). The majority of the patients were not in need of inpatient care or intensive treatment, as reflected by the low PANSS scores at both time points and the proportion of patients in remission. At baseline, 54 patients were receiving AP medication with a mean dosage in terms of standard haloperidol equivalents of 5.4 milligrams (mg) (SD = 3.4). At follow-up, 45 patients used AP medication (second generation: $n = 42$; first generation: $n = 3$), with a mean dosage of 4.7 mg (SD = 5.1). The lifetime cumulative AP exposure was 13079.7 mg (SD = 10977.2).

The proportion of baseline scans with 76 directions did not differ between the groups (84% in controls, 82% in siblings, and 71% in patients: $\chi^2 = 3.02$, $df = 2$, $P = .22$).

Whole Brain Group Differences in FA Change Over Time (ΔFA)

The mean ΔFA revealed a slight increase over time in the controls (0.001) and a decrease over time in the siblings (−0.003) and patients (−0.0002), with the mean FA (0.504) of the siblings at follow-up in between that of the controls (0.509) and the patients (0.502) (figure 1). At follow-up, there were more WM tracts showing a decrease than an increase in patients and siblings (27 and 23 of the 38 tracts, respectively), whereas in controls the proportion of decreases and increases was balanced (table 2).

There was no significant association between group and ΔFA ($\chi^2 = 4.9$, $df = 2$, $P = .09$). Although the direction of effect for patients compared to controls indicated a decrease in FA over time, the difference was not significant ($B = -0.002$, $P = .19$); additional correction for last year cannabis use, lifetime cannabis use, and scan type did not change the results of the patient-control comparisons ($B = -0.002$, $P = .22$; $B = -0.002$, $P = .30$ and $B = -0.002$, $P = .17$, respectively). In siblings compared to controls, there was a significant decrease in FA ($B = -0.004$, $P = .04$). This effect remained significant when controlled for scan type ($B = -0.004$, $P = .04$) and last year cannabis use ($B = -0.004$, $P = .04$), and close to significant when controlled for lifetime cannabis use ($B = -0.003$, $P = .07$) and history of depression ($B = -0.003$, $P = .06$). No significant group \times sex interaction in the model of ΔFA ($\chi^2 = 0.9$, $df = 2$, $P = .62$) was found.

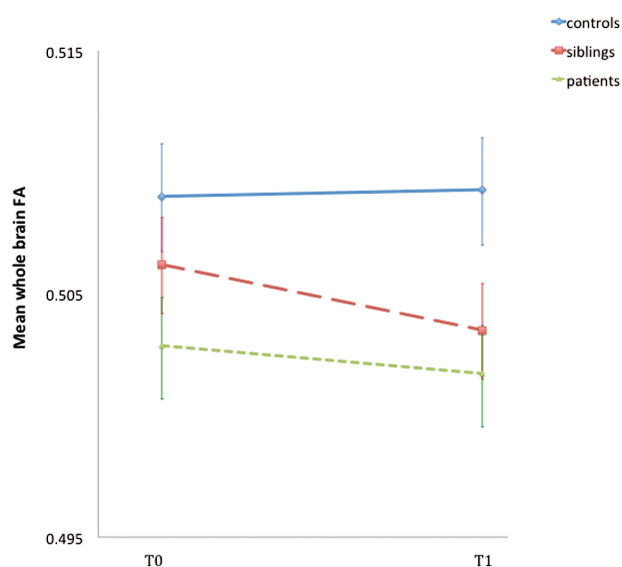


Fig. 1. Group differences in whole brain FA at follow-up. Error bars represent the SE of the mean ΔFA at baseline and at follow-up. FA, fractional anisotropy. For a color version, see this figure online.

Regional Group Differences in ΔFA

There was a significant group \times region interaction in the model of ΔFA ($\chi^2 = 105.4$, $df = 74$, $P = .01$), indicating that group differences varied as a function of region. The group factor was significant in 6 of the 38 regions, of which 4 regions survived after Simes' correction. Patients had a significant smaller FA increase in the right retrolenticular part of the internal capsule (RPIC), and a decrease in the right cingulum and the right posterior corona radiata (PCR) compared to controls. Siblings had a significant smaller FA increase in the right RPIC and a decrease in the right cingulum compared to controls. In comparison to patients and controls, siblings had a decrease in the left posterior thalamic radiation (PTR) (table 3, figure 2).

AP Medication

Within-patients analyses showed that there was a close to significant association between lifetime AP use (linear) and whole brain mean ΔFA ($B = -2.5 \times 10^{-7}$, $P = .08$). Compared to low lifetime AP exposure, patients with high AP exposure showed significantly more FA decrease over time ($B = -0.008$, $P = .04$), which was not the case for patients with moderate exposure ($B = -0.005$, $P = .15$). With regard to AP exposure over the last 3 years, a significant negative association was found between cumulative AP exposure (linear) and whole brain mean ΔFA over the last 3 years ($B = -5.6 \times 10^{-7}$, $P = .01$). Higher levels of AP medication over the last 3 years predicted a stronger decrease in FA: moderate vs low exposure: $B = -0.006$, $P = .04$; high vs low exposure ($B = -0.009$, $P = .004$).

The group analyses based on AP medication subgroups (low, moderate, and high cumulative AP medication exposure) showed that there was a significant decrease in FA over time in patients with the highest level of AP exposure (lifetime and over the last 3 years) compared to controls, but not in patients with moderate or low AP exposure. Siblings showed a significant stronger decrease in FA than patients with the lowest AP exposure (see supplementary table 1).

Whole Brain Group Differences in Mean FA at Follow-up

There was a significant association between group and FA at follow-up ($\chi^2 = 10.0$, $df = 2$, $P = .007$): siblings ($B = -0.007$, $P = .03$) and patients ($B = -0.010$, $P = .005$) showed a significantly lower mean FA compared to the controls. The sibling-patient comparison was neither large nor significant ($B = -0.001$, $P = .46$, figure 1).

Discussion

This longitudinal DTI study showed a relatively stable whole brain mean FA course in patients with schizophrenia after the critical phase (ie, >5 years of illness duration),

Table 2. Mean FA per Group at Baseline and at Follow-up

Brain Region	Mean FA								
	Controls			Siblings			Patients		
	T0	T1	Δ	T0	T1	Δ	T0	T1	Δ
Genu of corpus callosum	.7570	.7557	-.0012	.7551	.7515	-.0036	.7466	.7446	-.0020
Body of corpus callosum	.7214	.7216	.0003	.7175	.7155	-.0020	.7035	.7007	-.0028
Splenium of corpus callosum	.7877	.7915	.0037	.7891	.7873	-.0018	.7880	.7897	.0017
Forceps major	.7004	.7042	.0038*	.6974	.6956	-.0018	.6904	.6896	-.0009
Forceps minor	.5850	.5848	-.0002	.5827	.5800	-.0026	.5785	.5779	-.0006
Fornix (column and body)	.5278	.5199	-.0078	.5305	.5208	-.0097	.4812	.4855	.0043
Anterior limb of internal capsule, right	.6311	.6213	-.0098*	.6242	.6154	-.0088*	.6215	.6129	-.0086*
Anterior limb of internal capsule, left	.6083	.6194	.0111*	.6024	.6102	.0079*	.6003	.6116	.0113*
Posterior limb of internal capsule, right	.6949	.6903	-.0046	.6924	.6859	-.0065*	.6954	.6906	-.0048
Posterior limb of internal capsule, left	.6934	.6942	.0008	.6917	.6903	-.0014	.6977	.6953	-.0024
Retrolenticular part of internal capsule, right	.5807	.5993	.0186*	.5819	.5901	.0082	.5834	.5901	.0066
Retrolenticular part of internal capsule, left	.5985	.5883	-.0102*	.5951	.5859	-.0092*	.5935	.5902	-.0033
Anterior corona radiata, right	.5192	.5119	-.0073	.5150	.5043	-.0108*	.5056	.4947	-.0110*
Anterior corona radiata, left	.5037	.5084	.0047	.4979	.4980	.0002	.4885	.4942	.0057
Superior corona radiata, right	.5267	.5297	.0030	.5239	.5240	.0001	.5186	.5191	.0006
Superior corona radiata, left	.5319	.5207	-.0111*	.5261	.5169	-.0091*	.5235	.5121	-.0114*
Posterior corona radiata, right	.5172	.5115	-.0057	.5094	.4945	-.0150*	.5062	.4873	-.0189*
Posterior corona radiata, left	.5010	.5134	.0125*	.4892	.5018	.0125*	.4835	.4999	.0163*
Posterior thalamic radiation, right	.6269	.6260	-.0009	.6207	.6162	-.0045	.6180	.6081	-.0099
Posterior thalamic radiation, left	.6179	.6255	.0076	.6105	.6094	-.0011	.6011	.6123	.0111
Sagittal stratum ^a , right	.5732	.5744	.0012	.5687	.5637	-.0050	.5656	.5635	-.0020
Sagittal stratum ^a , left	.5706	.5746	.0040	.5609	.5625	.0016	.5617	.5641	.0024
External capsule, right	.4769	.4770	.0001	.4741	.4690	-.0050	.4711	.4679	-.0032
External capsule, left	.4731	.4755	.0024	.4679	.4698	.0020	.4652	.4715	.0063
Cingulum (cingulate gyrus), right	.6104	.6403	.0299*	.6099	.6333	.0233*	.6072	.6378	.0305*
Cingulum (cingulate gyrus), left	.6391	.6048	-.0343*	.6344	.6016	-.0328*	.6344	.6023	-.0320*
Cingulum (hippocampus), right	.5556	.5585	.0029	.5602	.5393	-.0210*	.5535	.5445	-.0090
Cingulum (hippocampus), left	.5486	.5702	.0216*	.5421	.5552	.0131	.5417	.5599	.0182*
Fornix, stria terminalis, right	.5581	.5806	.0225*	.5547	.5701	.0153*	.5454	.5671	.0217*
Fornix, stria terminalis, left	.5625	.5562	-.0063	.5590	.5433	-.0156*	.5509	.5426	-.0084
Superior longitudinal fasciculus, right	.5298	.5313	.0015	.5325	.5297	-.0028	.5320	.5241	-.0079
Superior longitudinal fasciculus, left	.5303	.5243	-.0060	.5305	.5258	-.0047	.5271	.5233	-.0038
Superior fronto-occipital fasciculus, right	.5380	.5308	-.0072	.5329	.5281	-.0048	.5214	.5155	-.0060
Superior fronto-occipital fasciculus, left	.5276	.5252	-.0023	.5189	.5188	-.0001	.5097	.5123	.0026
Uncinate fasciculus, right	.5523	.5516	-.0006	.5393	.5413	.0019	.5395	.5387	-.0008
Uncinate fasciculus, left	.5263	.5179	-.0084	.5109	.5074	-.0035	.5071	.5108	.0037
Tapetum, right	.6164	.6121	-.0042	.5907	.5824	-.0083	.5910	.5714	-.0196*
Tapetum, left	.6345	.6343	-.0002	.6106	.5983	-.0124	.5942	.5812	-.0130

Note: Δ = mean FA difference (mean FA follow-up – mean FA baseline), with values in italics representing FA decreases and bold representing FA increases. FA, fractional anisotropy.

^aIncl. inferior longitudinal fasciculus and inferior fronto-occipital fasciculus.

*Results of a within-group paired *t*-test examining significant within group Δ FA differences per brain region ($P < .05$), accounting for a false discovery rate with the Simes' procedure (38 regions \times 3 groups) ($*P_{\text{Simes}} < .003$).

whereas a significant decline in mean FA was observed in siblings. The effect of group varied as a function of region, as indicated by a significant group by region interaction. Overall, there were more tracts showing a decrease than an increase over time in both patients and siblings, with a significant group difference in 4 WM tracts.

Findings in Patients

The study showed that, over a 3-year period, the overall mean FA remained stable in patients, being continuously

lower than the mean FA of controls and siblings. This data is partly in line with the results of the study by Mitelman and colleagues (2009), examining an older (than the present) sample (of ± 41 years) of patients with a diagnosis of schizophrenia and healthy controls, also showing a rather stable FA in patients, and a greater, probably normal age-dependent, FA decline over time in frontal, temporal, and parietal WM in healthy controls.²⁰

The results suggest that major WM alterations in patients may have occurred in the early stages of the

Table 3. Group Comparisons in Regions With a Significant Group Effect

Brain Region	Between-Group Effect	Patient-Control	Sibling-Control	Patient-Sibling
	(χ^2 , $df = 2$, P)	(B , P)	(B , P)	(B , P)
Retro-lenticular part of internal capsule, right	11.8, .003†	−0.01, .001*	−0.01, .008*	−0.003, .49
Posterior corona radiata, right	10.5, .005†	−0.01, .001*	−0.009, .03	−0.004, .29
Posterior thalamic radiation, right	9.0, .01	−0.01, .003	−0.004, .27	−0.007, .05
Posterior thalamic radiation, left	14.2, .0008†	0.004, .31	−0.009, .01*	0.01, .0003*
Cingulum, right	19.6, .0001†	−0.01, .01*	−0.02, 9.7×10^{-6} *	0.01, .05
Superior longitudinal fasciculus, right	9.4, .009	−0.01, .002	−0.004, 0.15	−0.005, .08

Note: The χ^2 and the P -values represent the significant results of the between-group factor analyses per region in multilevel modeling ($†P_{\text{Simes}} < .005$). B and P -values of the individual group comparisons are shown ($*P_{\text{Simes}} < .02$). Analyses are controlled for age, sex, handedness, level of education, and scan interval.

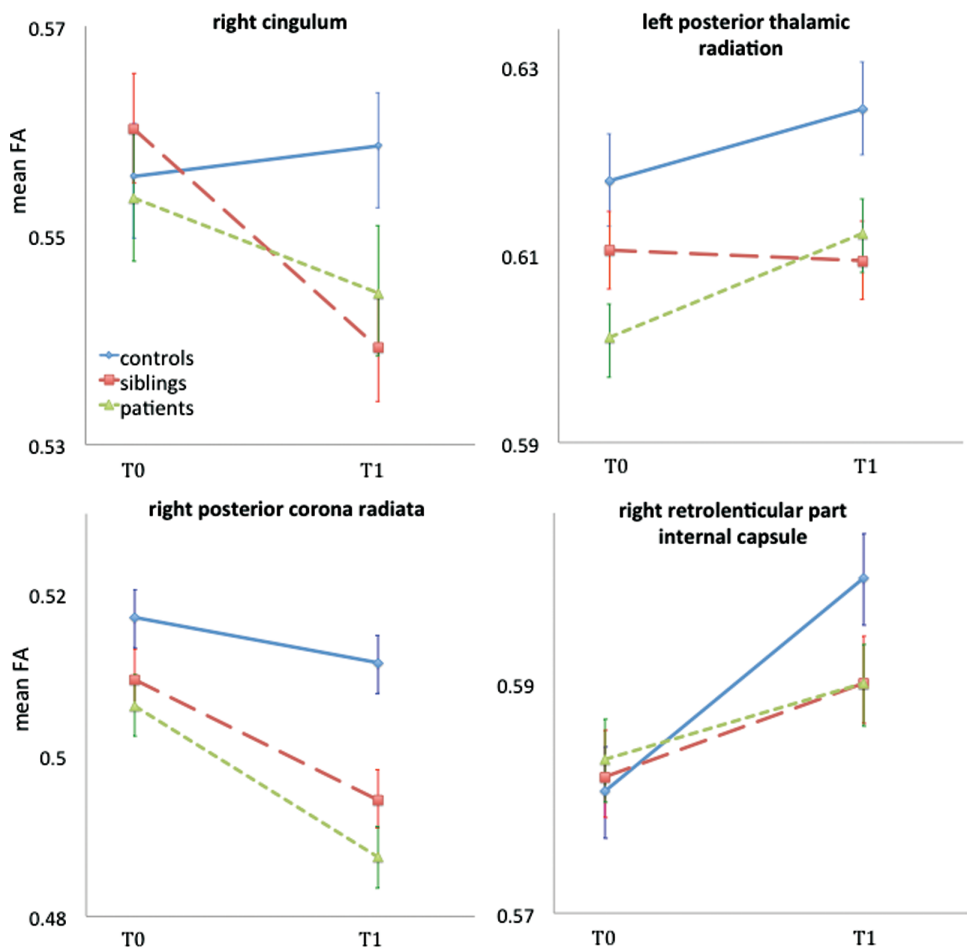


Fig. 2. Group \times region interactions in the model of Δ FA. Group differences in mean Δ FA in 4 WM tracts are displayed ($P_{\text{Simes}} < .02$), corresponding with table 3. Error bars represent the SE of the mean Δ FA at baseline and at follow-up. FA, fractional anisotropy. For a color version, see this figure online.

illness, as described previously,¹⁵ without ongoing progression. Alternatively, WM may have been modulated by AP medication, which was supported in the current study by the small but significant negative within-group effect of AP medication on Δ FA, with a dose-response effect for AP exposure over the last 3 years. Moreover, patients with the highest AP exposure levels (lifetime, as

well as over the last 3 years) had a significant decrease in FA over time compared to controls, whereas this was not the case for patients with low or moderate AP exposure compared to controls. Together with the widespread microstructural WM alterations presented in cross-sectional studies of at-risk populations and first episode psychotic patients,⁵ the data add

to the evidence for an early developmental origin of WM alterations in schizophrenia.⁸ Indeed, a significant progressive reduction in FA of the left frontal WM has been found in UHR subjects who later developed psychosis compared to UHR subjects who did not make the transition.¹⁷

Despite the overall mean FA being constant, most WM tracts in the 3 groups showed minor (nonsignificant) changes in individual FA trajectories (table 2). WM tracts develop at different ages in different curvilinear patterns (inverted U-shape), with FA increases from the newborn period to adolescence, shows decelerated maturation until mid-adulthood and subsequently displays more rapid decline during old age.^{40,41} The WM tracts of the controls in this study may be at the top of the normal age trajectory curve because of the proportionally equal number of WM tracts with an FA increase and decrease. In contrast, patients showed a higher number of WM tracts with FA decreases, suggesting an altered developmental pattern, ie, an earlier than expected age-related decrease of WM. Specifically, a smaller FA increase in the RPIC and decrease in the PCR and the cingulum (all right-sided) was found in patients. These tracts have face-validity, as they are frequently described in relation to fronto-temporal disconnection in schizophrenia.^{4,42}

Findings in Siblings

This is the first longitudinal study showing whole brain WM alterations over time in a sample of healthy participants at higher than average risk for psychotic disorder (siblings of patients with psychotic disorder). At baseline, there was no significant difference in whole brain mean FA between siblings and controls, whereas such a difference was apparent between siblings and patients.²⁴ At follow-up, siblings showed a significant lower whole brain mean FA with respect to the controls and the significant difference with patients was no longer apparent. The difference at follow-up was confirmed by a significant FA decrease over time in siblings compared to controls, which was not observed in patients. At the level of individual tracts, almost two-third of the WM tracts in siblings revealed a decrease in FA over time, compared to the more balanced ratio of FA increases and decreases in the controls. Specifically, the left PTR and the right cingulum revealed a significant decrease of mean FA over time in siblings, whereas controls showed an increase. The PTR has previously been associated with schizophrenia,^{15,43} eg, with impaired emotional self-awareness.⁴⁴ To our knowledge subtle FA decreases in the PTR have only been associated with bipolar⁴⁵ but not psychosis liability. As mentioned before, all WM tracts have different maturational trajectories.⁴⁶ The cingulum has one of the most prolonged maturation periods and reaches its peak FA only after 40 years of age.⁴⁷ Given the mean age of 34 years in the siblings and of 32 years in the patients, the earlier than expected FA decline may reflect disturbed

WM maturation from an early age, suggesting a neurodevelopmental origin. Alternatively, it may suggest progression associated with illness vulnerability, though the findings in the patients did not support this.

Decreased anisotropy in the cingulum has also been described in several cross-sectional studies in patients with schizophrenia^{48,49} and in the longitudinal study of Mitelman and colleagues (2009), where the left anterior cingulate gyrus was 1 of the 2 areas that showed a greater decline in FA in patients with schizophrenia compared to healthy participants.²⁰ Regarding the present finding of a patient-control difference in this region, current and previous cross-sectional DTI findings⁵⁰ in siblings may be suggestive of a WM intermediate phenotype.

Clinically, WM alterations in (sub-)regions of the cingulum have been related to impairments in impulsivity⁵¹ and executive functioning⁵² as well as to positive and negative symptoms⁵³ in patients with schizophrenia. As mild cognitive alterations are present in non-affected relatives,^{54,55} it may be hypothesized that subclinical expression of symptoms are associated with this WM intermediate phenotype, which will be the topic of further investigation.

Methodological Considerations

Although the present study has several strengths, such as the rather large sample size, the longitudinal design covering a 3-year period, and the inclusion of both patients and their healthy siblings, there are some limitations that need to be taken into account when interpreting the results.

AP medication may have an effect on WM.¹⁵ Until now, only a handful of longitudinal diffusion studies have been published, examining (short-term) effects of AP medication on microstructural WM (pre-post treatment measurements).^{56–59} The results of the present study were supportive of an effect of (especially the highest) cumulative medication exposure levels on FA change over time, both in within-patients analyses and in between-group analyses based on AP exposure subgroups (with one-third of the patients in each subgroup). However, as the FA change in siblings, who were not using AP medication, was also significantly different from controls, AP exposure may be one of the contributing factors of microstructural WM alteration in patients with psychotic disorder.

The same applies to drug use. The present study sample was not drug-free which may have influenced our results. Study results differ with respect to the potential influence of cannabis use on WM alterations in patients with schizophrenia.⁶⁰ Although the significant results in the control-sibling comparison remained stable after controlling for cannabis use (last year), lifetime cannabis use appeared to exert some influence, although the effect size was not affected much.

Given the absence of (1) differences in alcohol consumption across groups, (2) other drug use in the controls

and siblings, and (3) effects of other drug use on microstructural WM in the baseline study,²⁴ sensitivity analyses for these substances were not considered additional informative.

Inconsistencies in the results of the limited longitudinal studies conducted to date may be due to varying patient samples,^{17,20} as well as varying acquisition and analysing techniques. Although Reis Marques and colleagues (2012) used TBSS, their procedures and analyses differed from the present study.¹⁸ Furthermore, limited knowledge is available about the margins of across-session reproducibility errors.^{61,62} As this was the first longitudinal DTI study including healthy siblings, we used a whole brain, voxel-based analyses, given the fact that evidence for differential WM regional time-trajectories is missing to date. The results of the group by region interactions are thus hypothesis-generating and may be of use in future longitudinal studies that examine individual WM tracts within distinct development trajectories.

Supplementary Material

Supplementary material is available at <http://schizophreniabulletin.oxfordjournals.org>.

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